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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/650,112	MARKOWITZ, SANFORD D.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

RD

DETAILED ACTION

1. The election filed February 10, 2005 is acknowledged and has been entered. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-27 are pending in the application. Claims 1-21 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 22-27 are currently under prosecution.

Specification

4. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figures 34 and 35 are not identified by sequence identification numbers, either in the figure or in the brief descriptions of figures at page 19. In addition, there is a sequence disclosed at page 77, line 14, which is not identified.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

5. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such improperly demarcated trademarks is GenBank™ (page 36, line 11, and elsewhere) and BiaCore™ (page 47, line 18).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

6. The specification is objected to because of the following informality:

At page 11, lines 8-10, the specification reads, "the secreted ColoUp1 polypeptide is selected from among: a) a secreted polypeptide produced by the expression of a nucleic acid that is at least 95% identical to the amino acid sequence of SEQ ID No: 4". SEQ ID NO: 4, however, is a polynucleotide sequence, not an amino acid sequence. Appropriate correction is required.

Claim Objections

7. Claims 22-27 are objected to because claim 27 is drawn in the alternative to the subject matter of non-elected inventions. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claims 22-27 are directed to a method for identifying a candidate agent for treating colon cancer comprising identifying a candidate agent that binds to and/or inhibits an activity of "ColoUp1".

The specification defines the term "ColoUpX" (e.g., ColoUp1) at page 21 as "a nucleic acid encoding a ColoUp protein or a ColoUp protein itself, as well as distinguishable fragments of such nucleic acids and proteins, longer nucleic acids and polypeptides that comprise distinguishable fragments or full length nucleic acids or polypeptides, and variants thereof" (lines 24-28). It continues, disclosing that said "[v]ariants include polypeptides that are at least 90% identical to the relevant human ColoUp SEQ ID Nos. referred to in the application, and nucleic acids encoding such variant polypeptides" (lines 28-30); and moreover, said variants include "different post-

translational modifications, such as glycosylations, methylations, etc." (lines 30 and 31). The specification discloses that "[p]articularly preferred variants include any naturally occurring variants, such as allelic differences, mutations that occur in a neoplasia and secreted or processed forms" (page 21, line 31, though page 22, line 2).

At page 11, lines 8-21, the specification further describes the term "ColoUp1" with the following disclosure:

> [T]he secreted ColoUp1 polypeptide is selected from among: a) a secreted polypeptide produced by the expression of a nucleic acid that is at least 95% identical to the amino acid sequence of SEQ ID No: 4; b) a secreted polypeptide produced by the expression of a nucleic acid that is a naturally occurring variant of SEQ ID No: 4; c) a secreted polypeptide produced by the expression of a nucleic acid that hybridizes under stringent conditions to a nucleic acid sequence of SEQ ID No: 4; d) a secreted polypeptide having a sequence that is at least 95% identical to the amino acid sequence of SEQ ID No: 1; and e) a secreted polypeptide having a sequence that is at least 95% identical to the amino acid sequence of SEQ ID No: 2. Optionally, the secreted ColoUp1 polypeptide is produced by the expression of a nucleic acid having a sequence that is at least 95%, 98, 99% or 100% identical to the nucleic acid sequence of SEQ ID No: 4. Preferably, the secreted ColoUp1 polypeptide has an amino acid sequence that is at least 95%, 98%, 99% or 100% identical to an amino acid sequence selected from among SEQ ID No: 1 and SEQ ID No:2.

Then, at page 12 (paragraph 4), the specification provides the following definition:

> The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

Accordingly, given the broadest, reasonable interpretation of the claims that is consistent with the supporting disclosure, the claims are directed to a genus of polypeptides comprising an amino acid sequence that is at least 90% identical to a sequence of SEQ ID NO: 3, wherein said sequence of SEQ ID NO: 3 constitutes a sequence of as few as two amino acids.

Therefore, the claims are directed to a genus of polypeptides that vary astoundingly structure. It follows, given the structurally disparate nature of the polypeptides to which the claimed antibodies bind, that the polypeptides vary substantially in function as well.

In contrast, the specification teaches only a few polypeptides, including the polypeptide of SEQ ID NO: 3; and given the structurally and functionally disparate natures of the genus of polypeptides, the disclosed polypeptides cannot be reasonably considered representative of the genus as a whole. Moreover, as the structures and functions of the polypeptides vary so, there is no correlation between any one particularly identifying structural feature that is common to at least a substantial number of the members of the genus and any one particularly identifying functional feature. As such, the skilled artisan could not immediately envision, recognize, or distinguish members of the genus of polypeptides to which the claimed antibodies bind. For this reason, the supporting disclosure would not reasonably convey to skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Even were the claimed polypeptides limited to those having amino acid sequences that are at least 90% identical to *the* amino acid sequence set forth as SEQ ID NO: 3, the skilled artisan could not immediately envision, recognize, or distinguish the antibodies because the skilled artisan could not immediately envision, recognize, or distinguish the polypeptides. The primary reason for this is that the polypeptides have not been described as sharing any particularly identifying functional feature. So, even if it were possible to list each and every species of polypeptide having amino acid sequences that are at least 95% identical to the amino acid sequence set forth as SEQ ID NO: 3, the skilled artisan could not recognize or distinguish those that are part of the invention from others.

Even were the polypeptides described as related by a particularly identifying common functional feature, the supporting disclosure would not be adequate to enable the skilled artisan to envision, recognize or distinguish the antibodies that bind to at least a substantial number of the members of genus of structurally disparate polypeptides, since the supporting disclosure does not include a description of the amino acid residues that can or cannot be changed, and if so, by which other amino acids, such that variants of the polypeptide of SEQ ID NO: 3 would retain its function. The description of a broad structural similarity alone does not suffice to accurately and reliably describe those particular amino acid residues that are functionally important or

essential. Skolnick et al. (*Trends in Biotechnology*. 2000; **18**: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a variant of the polypeptide of SEQ ID NO: 3 is capable of functioning the same, or even as having the same structure as the polypeptide of SEQ ID NO: 3.

Furthermore, as the claims are drawn to a method for identifying an agent (e.g., an siRNA molecule, an antisense oligonucleotide, an antibody, or a small molecule) that binds to and inhibits an activity of a member of the genus of "ColoUp1" polypeptides to which the claims are directed, it is aptly noted that because an activity of the various different members of the genus of polypeptides has not been described, the supporting disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. "[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes an agent that can be used, or should be considered a candidate for use in achieving a therapeutic effect in patients afflicted with colon cancer. Moreover, the supporting disclosure provides no description of a correlation between either the presence of, or the activity of any one of the members of the genus of polypeptides to which the claims are directed and the etiology or pathology of colon cancer that would reasonably suggest that an agent that binds to and/or inhibits an activity of the polypeptides should be regarded as "a candidate agent for treating colon cancer". While the gene encoding the polypeptide of SEQ ID NO: 3 may be over-expressed in colon cancer, relative to the gene present in normal colon

cells, this fact alone should not be considered objective evidence of the assertion that an agent that binds to and/or inhibits the activity of the polypeptide may be therapeutically useful in treating colon cancer. It is submitted that until it has been demonstrated that a reduction in the level of expression or activity of any of these proteins causes, for example, growth inhibition in colon cancer cells over-expressing the gene encoding the protein that it would be premature to conclude that identifying agents that bind to and/or inhibit its activity should be considered candidates for treating colon cancer.

Moreover, given that the specification discloses that the polypeptide of SEQ ID NO: 3 is secreted by colon cancer cells, it is sensible to question the reasonableness of the assertion that such molecular-target-based drugs will be therapeutically effective. There are examples of "tumor-associated antigens" that are aberrantly expressed by cancer cells relative to normal cells of the same tissue type, which, although are diagnostically useful, are not considered therapeutically useful molecular targets. As recently reviewed by Gray (*Clin. Lab.* 2005; **51** (3-4): 127-133), prostate-specific antigen (PSA) is such an antigen. Like the polypeptide of SEQ ID NO: 3, PSA is secreted by prostate cancer cells into the serum of patients afflicted by the disease. While PSA is diagnostically useful as a "tumor marker", it has not been thought a reasonable target for molecular-target-based drugs, which is not to say that it might not be sensible to design a drug capable of reducing the expression of the gene encoding PSA, since it PSA may have a role in regulating the growth of prostate cancer cells, which has yet to be discovered. Rather, the implication is that it would not be sensible to try to target cancer cells with an agent that binds to and/or inhibits the activity of a tumor antigen that is secreted and not retained by the cells expressing the gene encoding the antigen. By way of further explanation, a radioimmunoconjugate, for example, comprising antibody that binds "ColoUp1", which is secreted by colon cancer cells, binds the protein in the serum of a patient afflicted with the disease; however, because the protein is secreted, it would not be expected to effectively target the cancer cells that produce the protein.

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). In this instance, the supporting disclosure asserts that an agent that binds to and/or inhibits any member of the genus of structurally and functionally disparate polypeptides to which the claims are directed may be regarded as "a candidate agent for treating colon cancer". While the specification discloses that the polypeptide of SEQ ID NO: 3 is over-expressed in colon cancer, relative to normal colon cells, it has not described a correlation of the level of expression of other members of the genus of polypeptides with the presence of colon cancer. In fact, as illustrated by De Plaen et al. (*Immunogenetics.* 1994; **40**: 360-369), for example, the skilled artisan cannot predict whether a variant of the polypeptide of SEQ ID NO: 3 will be found to be associated with colon cancer and moreover, whether an agent that binds to and/or inhibits an activity of such a variant can be considered "a candidate agent for treating colon cancer". De Plaen et al. reviews the structure, chromosomal localization and expression of twelve genes encoding members of the MAGE family of proteins; see entire document (e.g., the abstract). De Plaen et al. teaches six of the members of the gene family were found to be expressed at a high level in a number of tumors of various histological types; while five were very weakly expressed in all samples tested, and one, namely MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (page 367, column 1). Just as not all members of the MAGE family of proteins are associated with cancer, particularly, since is it not obvious what, if any, association the weakly expressed MAGE proteins have, it is apparent that the skilled artisan cannot predict, based upon the information disclosed in the specification, whether variants of the polypeptide of SEQ ID NO: 3, as members of a presumed family of structurally related proteins, have an association with the etiology or pathology of colon cancer (e.g., whether the genes encoding such variants are overexpressed in colon cancer). Of course, if one would not accept the assertion that a variant of the polypeptide of SEQ

ID NO: 3 is associated with colon cancer merely upon the basis of its structural similarity to the polypeptide of SEQ ID NO: 3, one would not accept the assertion that an agent that binds to and/or inhibits an activity of the variant should be considered "a candidate agent for treating colon cancer".

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (*supra*) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus.. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

10. Claims 22-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for identifying a candidate agent for treating colon cancer. As explained above, the claims are directed to a genus of polypeptides having widely varying structures and functions.

The specification teaches that the genes encoding a few polypeptides, such as the polypeptide of SEQ ID NO: 3 are overexpressed in colon cancer.

The amount of guidance, direction, and exemplification set forth in the specification would not sufficient to enable the skilled artisan to make and use the claimed invention without undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As the claims are directed to a genus of structurally and functionally different proteins, the supporting disclosure would not be adequate to enable the skilled artisan to use the claimed invention. Although the polypeptide of SEQ ID NO: 3 may be overexpressed in colon cancer, the skilled artisan cannot predict which of the many polypeptides encompassed by the claims are also overexpressed in colon cancer.

Again, De Plaen et al. (*supra*) teaches that even among closely related protein family members, the skilled artisan cannot predict whether a particular member of the family is associated with the etiology or pathology a specific disease, solely on the basis that another member of the family has been shown to be.

Considering the vastly different structures and functions of the members of the genus of polypeptides, it is reasonably expected that most of claimed polypeptides could not be used in a manner taught by the supporting disclosure, since there is a reasonable expectation that most will not be overexpressed in colon cancer. If the

expression or activity of the polypeptide is not associated with the onset or progression of colon cancer, it is not reasonable to assert that an agent that binds to and/or inhibits an activity of the polypeptide is a candidate agent for treating colon cancer. The amount of guidance, direction, and exemplification set forth in the disclosure is not reasonably commensurate in scope with the claims.

Although the specification discloses the gene encoding the polypeptide of SEQ ID NO: 3 is overexpressed in colon cancer cells, relative to the same gene in normal colon cells, the specification does not describe an activity of the polypeptide. Inasmuch as the claims are drawn to a method for identifying an agent that binds to and/or inhibits an activity of the polypeptide of SEQ ID NO: 3, the skilled artisan could not use the claimed invention without undue experimentation because it would first be necessary to discover the activity or function of polypeptide and then develop an assay that might be used to identify an agent that binds to and inhibits its activity or function.

Inasmuch as the claims are drawn to a method for identifying an agent that binds to and/or inhibits an activity of a member of the structurally and functionally disparate members of the genus of "ColoUp1" polypeptides to which the claims are directed, even were the activity of the polypeptide of SEQ ID NO: 3 known or disclosed, the skilled artisan cannot predict the consequence of structural dissimilarity in the functions of structurally related proteins. Again, Skolnick et al. (*supra*) teaches that even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Bowie et al. (*Science*. 1990; **257**: 1306-1310) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn, utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to submit a complete list of the proteins, which fall within the scope of the present claims, the skilled

artisan could not recognize which of these would function similarly to a protein comprising the amino acid sequence of SEQ ID NO: 3, and which would not, even where the proteins only differ at a small number of positions within their sequences. Burgess et al. (*Journal of Cell Biology.* 1990; **111**: 2129-2138) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As yet another example of this sensitivity, Lazar et al. (*Molecular and Cellular Biology*, 1988; **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* type amino acid substitution may adversely affect the function of a protein. As such, even were the function of the polypeptide of SEQ ID NO: 3 known, the skilled artisan could not use the claimed invention without undue experimentation, since the skilled artisan would have to empirically determine whether the expression and/or activity of a variant of the polypeptide of SEQ ID NO: 3 has or retains that function and whether the expression and/or function of the variant is associated with the onset, growth, or progression of colon cancer expressing the variant, such that the claimed invention could be used to identify "a candidate for treating colon cancer" by identifying an agent that binds to and/or inhibits the expression or activity of the variant.

Furthermore, the purpose of practicing the claimed invention is to identify a candidate agent for treating colon cancer. While the specification discloses that the gene encoding the polypeptide of SEQ ID NO: 3 is over-expressed in colon cancer, relative to the same gene in normal colon cells, it fails to establish a correlation between the expression or activity of the polypeptide, or any variant thereof to which the claims are directed, and the onset, growth, or progression of colon cancer, so as to provide a scientifically sound rationale for identifying candidate agents for treating colon cancer using the claimed invention. As explained above, because the specification discloses the polypeptide of SEQ ID NO: 3 is secreted from colon cancer cells, it is sensible to

question the reasonableness of the assertion that molecular-target-based drugs identified by practicing the claimed invention will be therapeutically effective, or even considered "candidates agents" for treating colon cancer. It is submitted that until it has been demonstrated that a reduction in the level of expression or activity of any of these proteins causes, for example, growth inhibition in colon cancer cells over-expressing the gene encoding the protein that it would be premature to conclude that identifying agents that bind to and/or inhibit its activity should be considered candidates for treating colon cancer. The need to first validate the speculative presumption that the members of the genus of polypeptides to which the claims are directed do, in fact, have functional roles in colon cancer, which if antagonized or inhibited might be yield a therapeutically beneficial effect, would constitute a need to perform undue experimentation.

The claims would merely serve as an invitation to one skilled in the art to determine whether there *is* a rationale for identifying a candidate agent for treating colon cancer by identifying an agent that binds to and/or inhibits a member of the genus of "ColoUp1" polypeptides to which the claims are directed.

As a final note, although the specification discloses that colon cancer cells express a relative abundance of the messenger RNA (mRNA) molecules encoding the polypeptide of SEQ ID NO: 3 and secrete the polypeptide (e.g., page 71, line 12, through page 72, line 9), the specification has not disclosed that the amount of the polypeptide secreted by the cells is concordant with the amount of mRNA produced by the cell. It is well established one cannot predict whether the level of protein produced by a cell will reflect the amount of mRNA produced by the cell: "But having acknowledged that control of gene expression can occur at multiple stages, *and that production of RNA cannot inevitably be equated with production of protein*, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription" (italicized for emphasis) (Genes VI, 1997; Ed. Benjamin Lewin; Chapter 29, first page). As further emphasized by the teachings of Chen et al. (*Molecular & Cellular Proteomics.* 2002; **1**: 304-313), one cannot merely presume that, because there is an association between the amount of mRNA produced by a given sample of cells and the presence of cancer, the amount of protein encoded by that mRNA may also

associated with the presence of cancer in the sample. Chen et al. teaches expression of protein and mRNA in cancer are discordant; see entire document (e.g., the abstract). Liu et al. (*Cancer J.* 2001 Sep-Oct; **7** (5): 395-403) shows similarly that the amplification of the gene encoding HER-2, another tumor-associated antigen, which often leads to over-expression, does not necessarily correlate with over-expression. Liu et al. shows that amplification of the gene encoding HER-2 was detected in a substantial portion of prostate cancer cells that do not over-express the protein; see entire document (e.g., the abstract). For this additional reason, because the effectiveness of many molecular-target-based drugs (e.g., immunotoxins) rely on the tendency of the targeted cancer cells to express an abundance of the protein to which the drug binds, relative to other types of cells, the claimed invention can be used without undue amount of experimentation, because it would first be necessary to determine if the "ColoUp1" polypeptide, as opposed to the mRNA molecule encoding the polypeptide, is over-expressed and moreover, whether it is expressed by cells outside of the colon. This issue is relevant in this instance, since the results of such determinations would either tend to support or contradict the assertion that an agent that binds to and/or inhibits an activity of a "ColoUp1" polypeptide is a candidate agent for treating colon cancer.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification contained in the supporting disclosure would not be sufficient to enable the skilled artisan to use the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty

defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 22 and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication No. 2004/0005563 A1.

Claims 47-55 are drawn to a method for identifying a candidate agent comprising identifying an agent that binds to and/or inhibits an activity of ColoUp1.

As explained above, "ColoUp1" refers to a member of a genus of polypeptides that includes a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 3.

U.S. Patent Application Publication No. 2004/0005563 A1 (Mack et al.) teaches a polypeptide comprising an amino acid sequence that is identical to the amino acid sequence set forth as SEQ ID NO: 3; see entire document (e.g., SEQ ID NO: 95). Mack et al. teaches screening molecules and compounds, including antibodies and small molecules to identify those that bind to and inhibit the activity of the polypeptide (e.g., paragraph [0012], paragraphs [0035]-[0047]; paragraph [0051]; paragraph [0054]; and paragraphs [0223]-[0317]). Mack et al. teaches the molecules and compounds that are screened include RNAi molecules, antisense molecules, antibodies, and small organic molecules (e.g., paragraph [0106]; paragraph [0116]; paragraph [0200]; paragraph [0205]; paragraph [0207]; and paragraph [0232]).

13. Claims 22-27 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application Publication No. 2003/0235820 A1.

Claims 47-55 are drawn to a method for identifying a candidate agent comprising identifying an agent that binds to and/or inhibits an activity of ColoUp1.

As explained above, "ColoUp1" refers to a member of a genus of polypeptides that includes a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 3.

U.S. Patent Application Publication No. 2004/0235820 A1 (Mack et al.) teaches a polypeptide comprising an amino acid sequence that is identical to the amino acid

sequence set forth as SEQ ID NO: 3; see entire document (e.g., SEQ ID NO: 16). Mack et al. teaches screening molecules and compounds, including antibodies and small molecules to identify those that bind to and inhibit the activity of the polypeptide (e.g., paragraph [0006], paragraphs [0036]; paragraph [0037]; paragraph [0040]; and paragraphs [0207]-[0323]). Mack et al. teaches the molecules and compounds that are screened include antisense molecules, antibodies, and small organic molecules (e.g., paragraph [0026]; paragraph [0080]; paragraph [0092]; paragraph [0129]; pargraph [0215]; and paragraph [0308]). Mack et al. teaches the screening process comprises testing the effects of the molecules and compounds on colon cancer cells or cell lines or in mouse xenografts of such cells or cell lines (e.g., paragraph [241]; and paragraph [0284]).

Conclusion

14. No claim is allowed.

15. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. U.S. Patent Application Publication No. 2004/0002120 A1 teaches a method for screening molecules to identify a molecule that binds to and/or inhibits a polypeptide comprising an amino acid sequence that is identical to the amino acid sequence set forth in the instant application as SEQ ID NO: 3.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
May 6, 2005

Notice to Comply	Application No.	Applicant(s)	
	10/650,112	MARKOWITZ, SANFORD D.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: If necessary to correct the deficiency noted in the Office action, Applicant must submit substitute copies of the Sequence Listing together with the amendment and statement described below.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
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